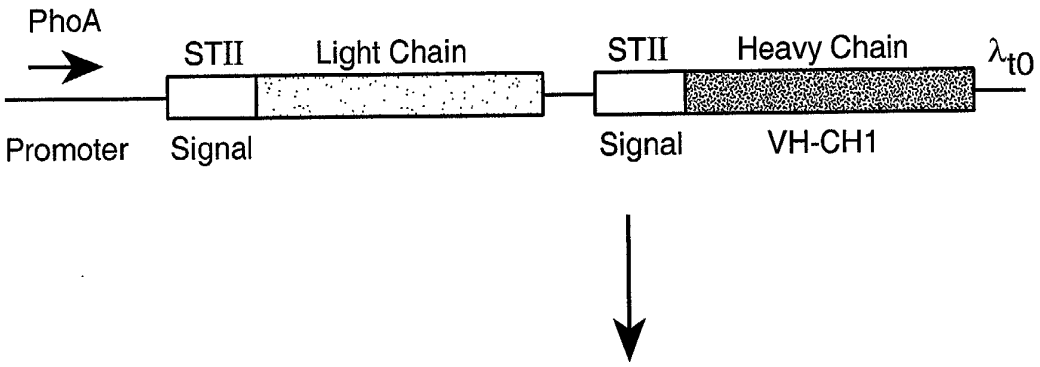
Fab Expression Vector pAK19



Full Length Antibody Expression Vector Derived from pAK19

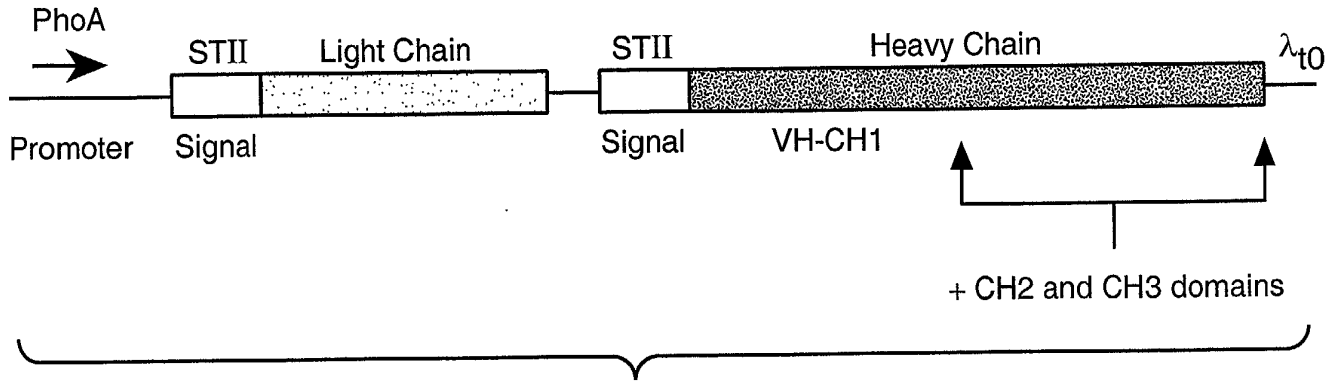


FIG._1

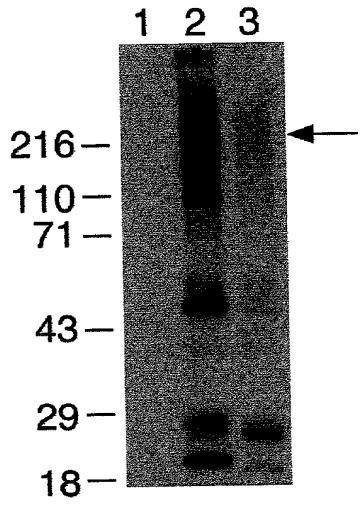

1 2 3
216
110
71
43
29
18

FIG._2

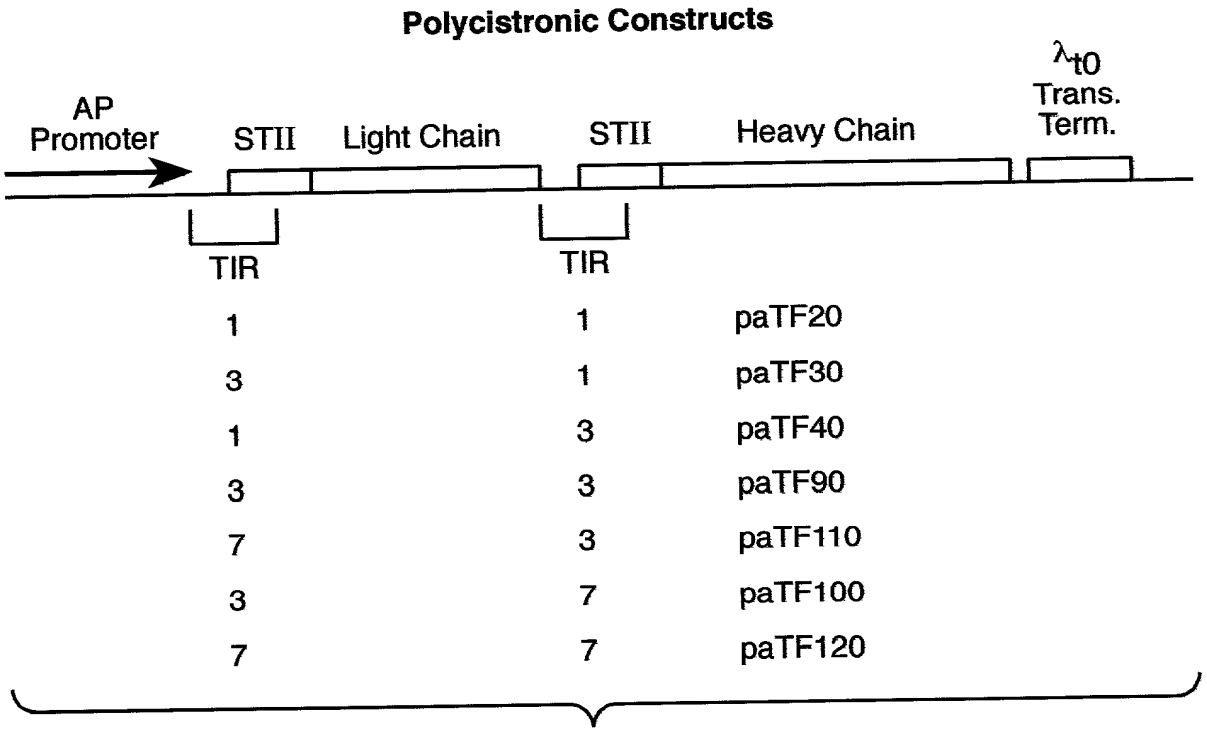

Polycistronic Constructs
AP Promoter
STII
Light Chain
STII
Heavy Chain
λ tO Trans. Term.
TIR
TIR
1 1 paTF20
3 1 paTF30
1 3 paTF40
3 3 paTF90
7 3 paTF110
3 7 paTF100
7 7 paTF120

FIG._3

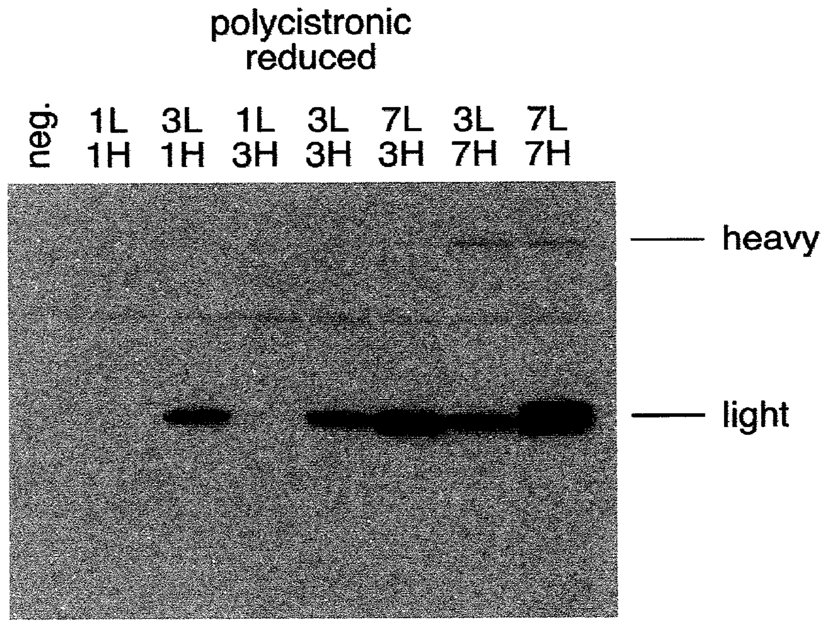


FIG._4A

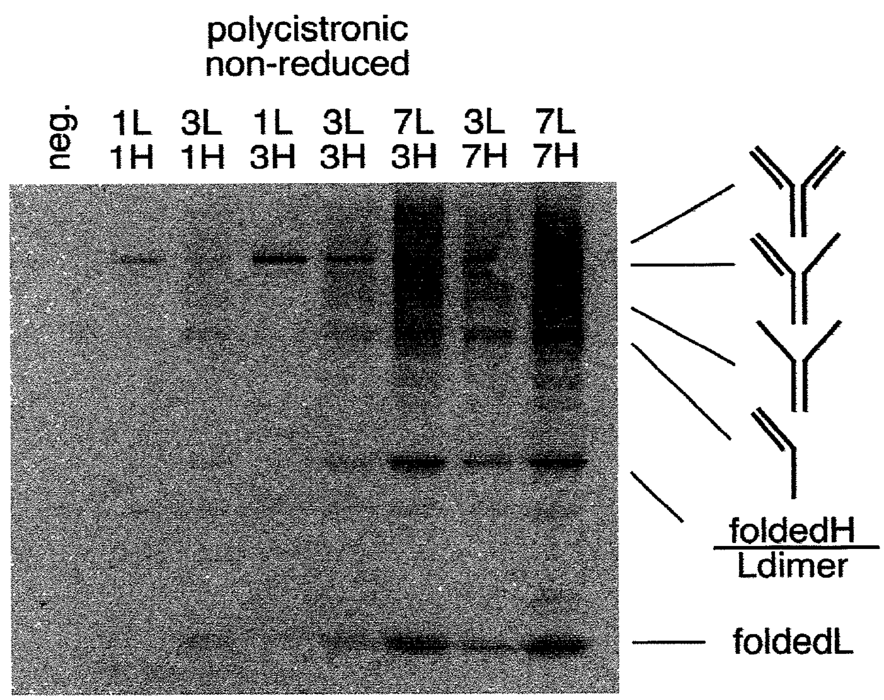


FIG._4B

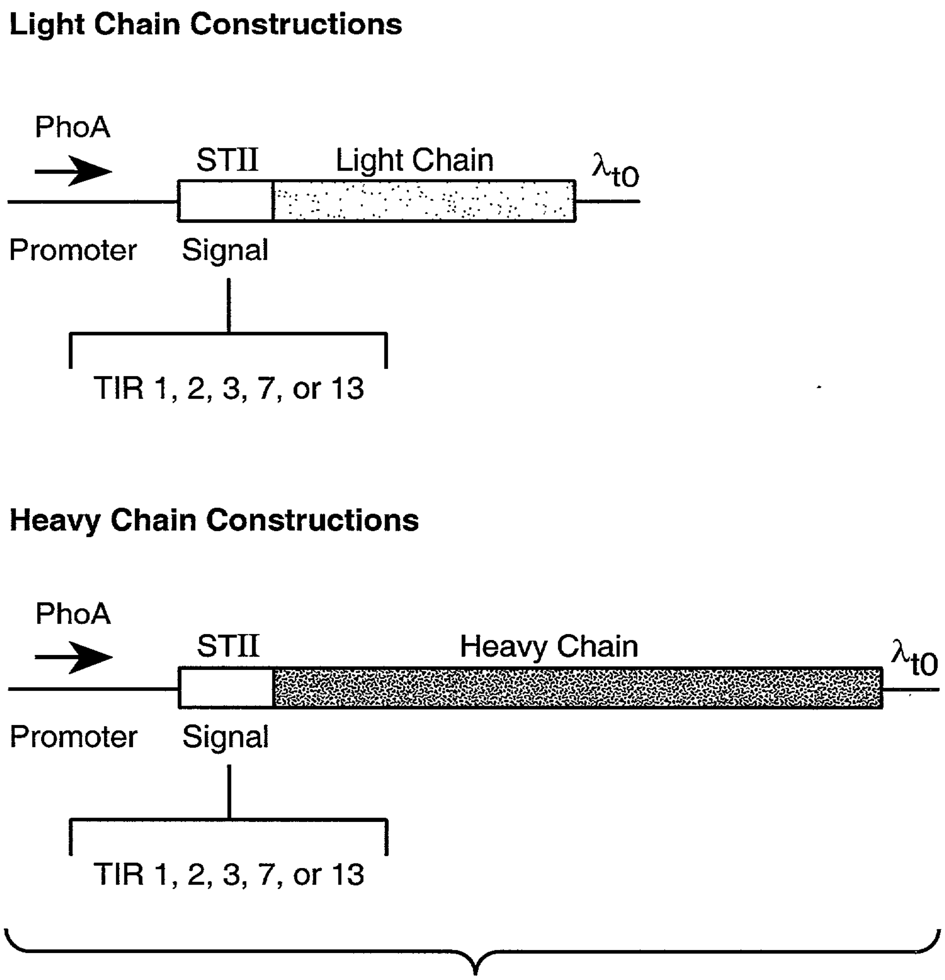


FIG._5

FIG._6A

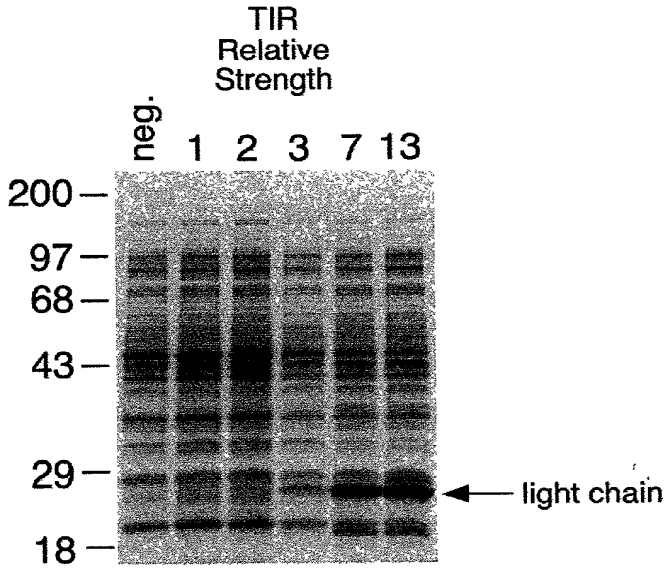


FIG._6B

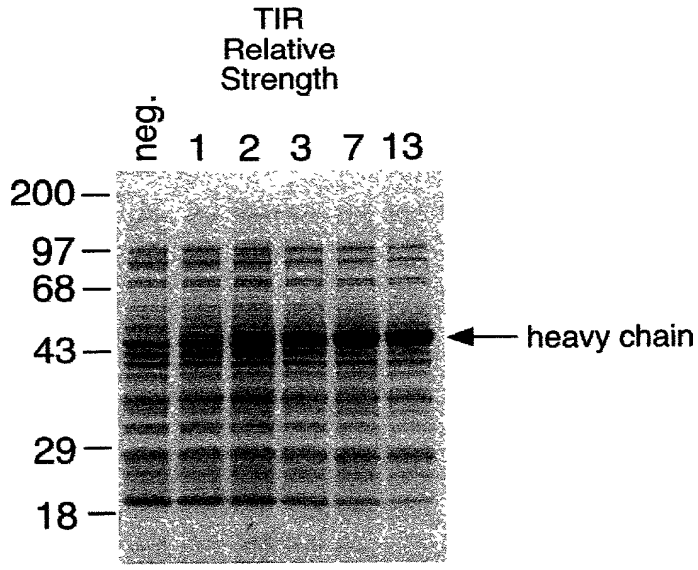
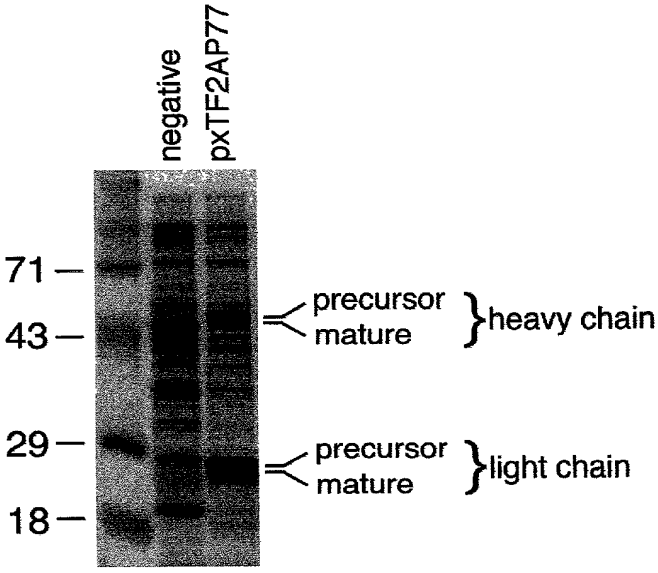


FIG._8



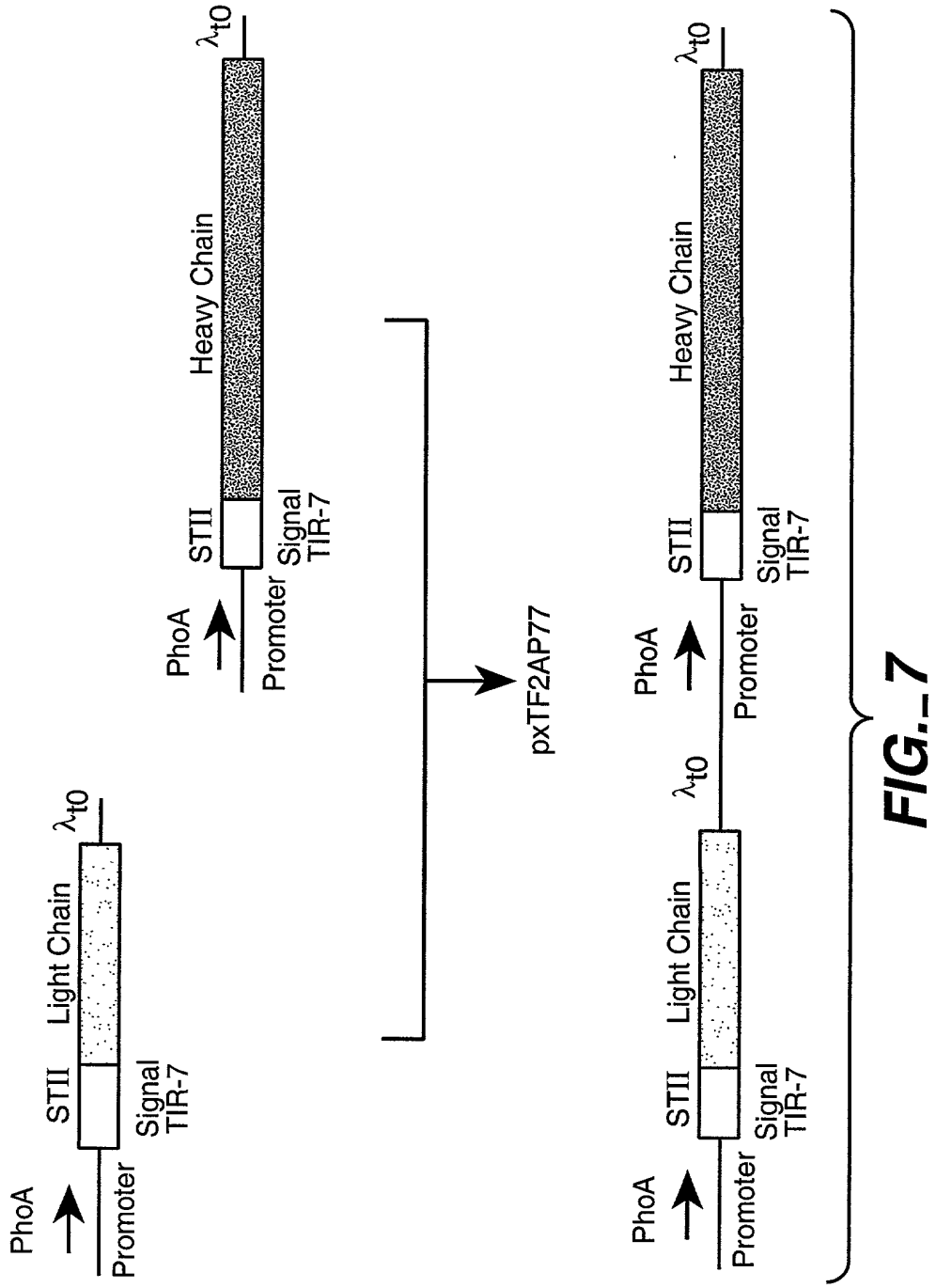
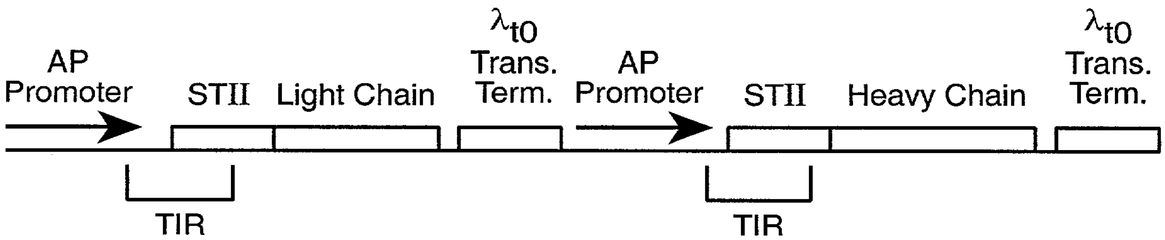

PhoA
Promoter
STII
Signal
Light Chain
λ_{t0}
pxTF2AP77
PhoA
Promoter
STII
Signal
Heavy Chain
λ_{t0}
PhoA
Promoter
STII
Signal
Light Chain
λ_{t0}
PhoA
Promoter
STII
Signal
Heavy Chain
λ_{t0}

FIG._7

Separate Cistron Constructs



1	1	paTF50
3	1	paTF70
1	3	paTF60
3	3	paTF80
7	3	paTF130
3	7	paTF140
7	7	paTF2AP77

FIG._9

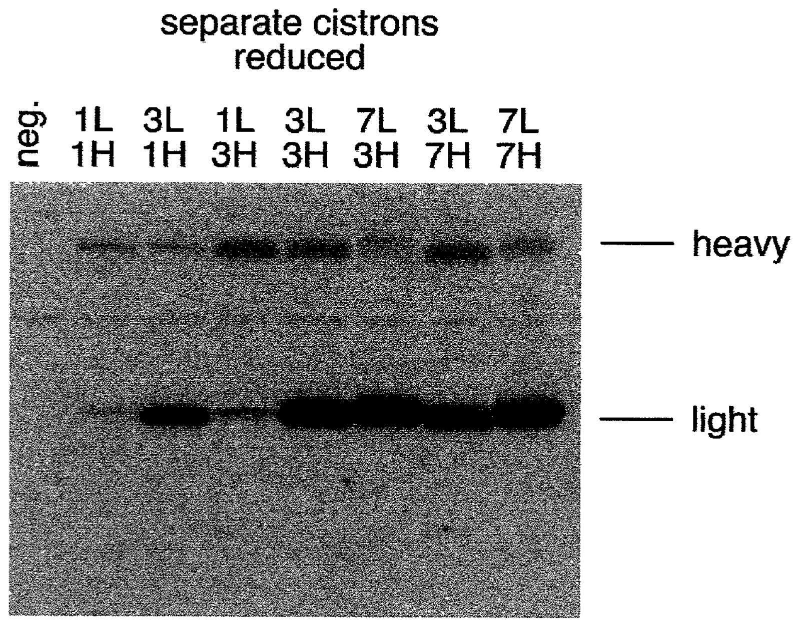


FIG._10A

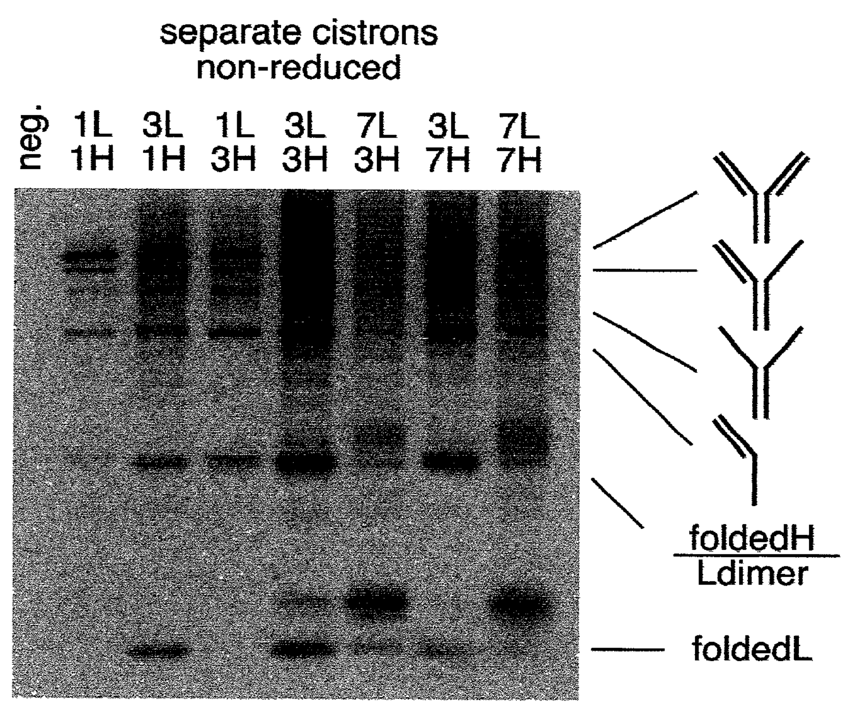
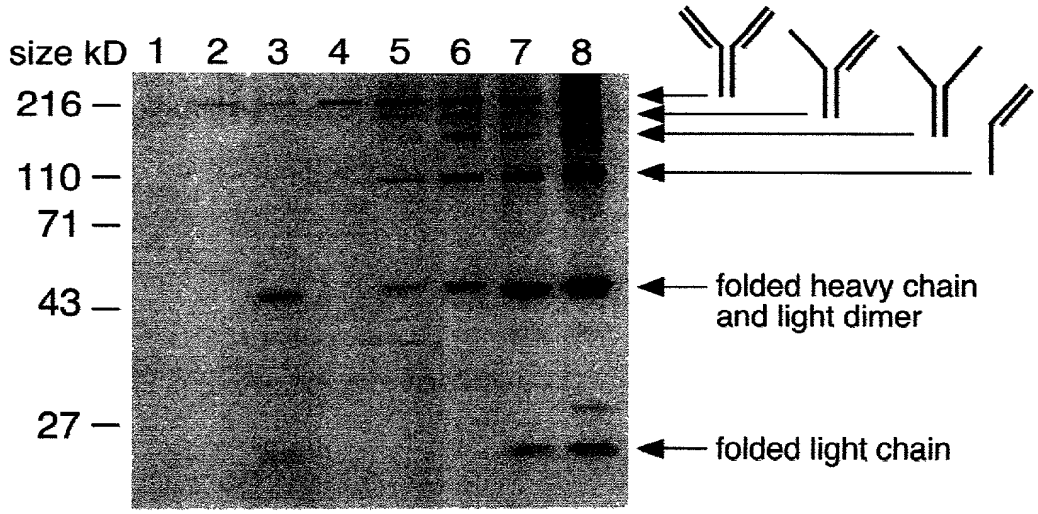


FIG._10B



1) negative control
2) TIR 1-light, TIR 1-heavy, polycistronic
3) TIR 3-light, TIR 1-heavy, polycistronic
4) TIR 1-light, TIR 3-heavy, polycistronic
5) TIR 1-light, TIR 1-heavy, separate cistrons
6) TIR 1-light, TIR 3-heavy, separate cistrons
7) TIR 3-light, TIR 1-heavy, separate cistrons
8) TIR 3-light, TIR 3-heavy, separate cistrons

FIG._11

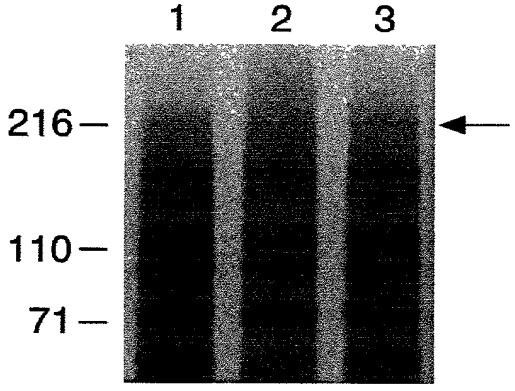


FIG._12

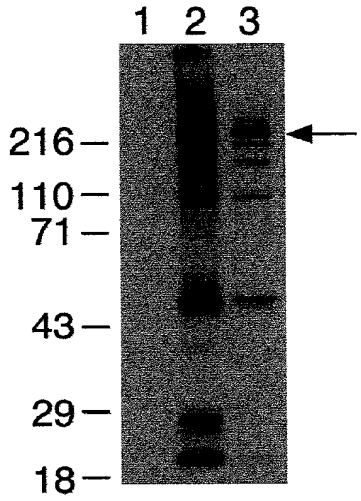


FIG._13

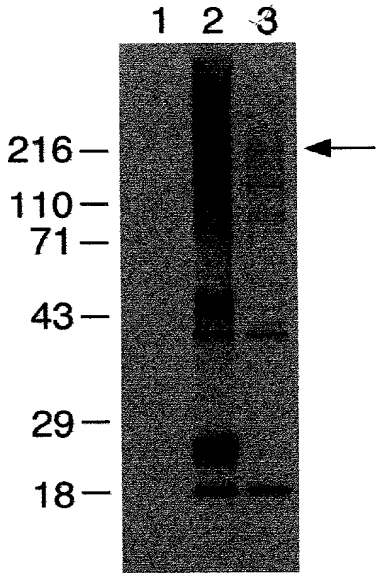


FIG._14

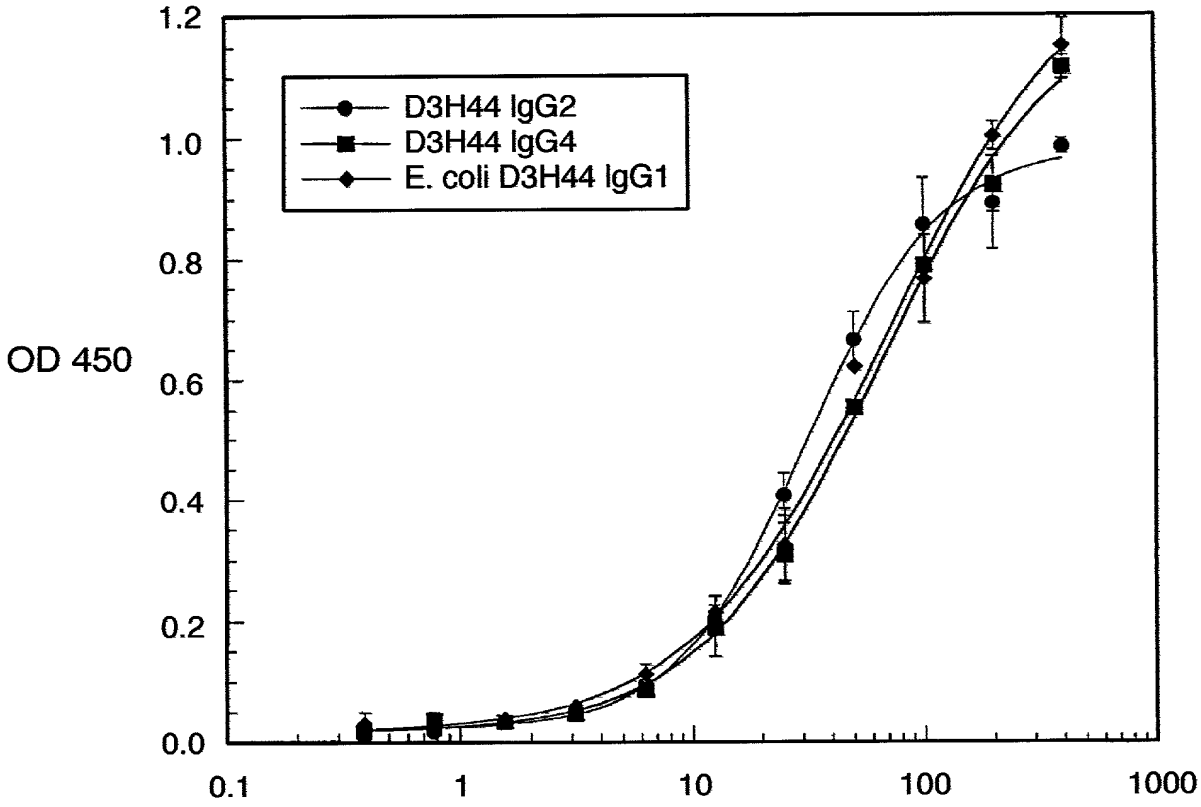


FIG._15

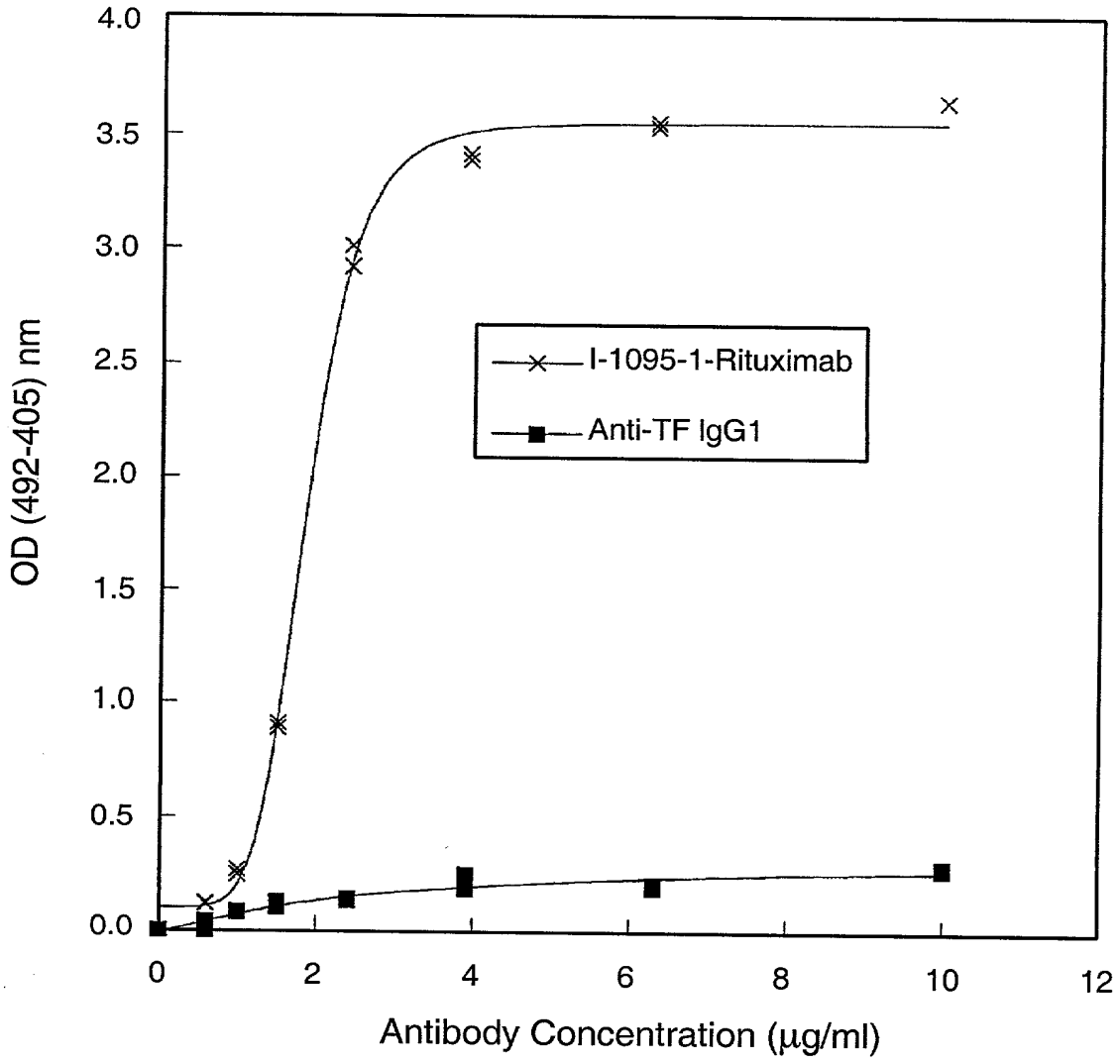

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OD (492-405) nm
0
2
4
6
8
10
12
Antibody Concentration (µg/ml)
I-1095-1-Rituximab
Anti-TF IgG1

FIG._16

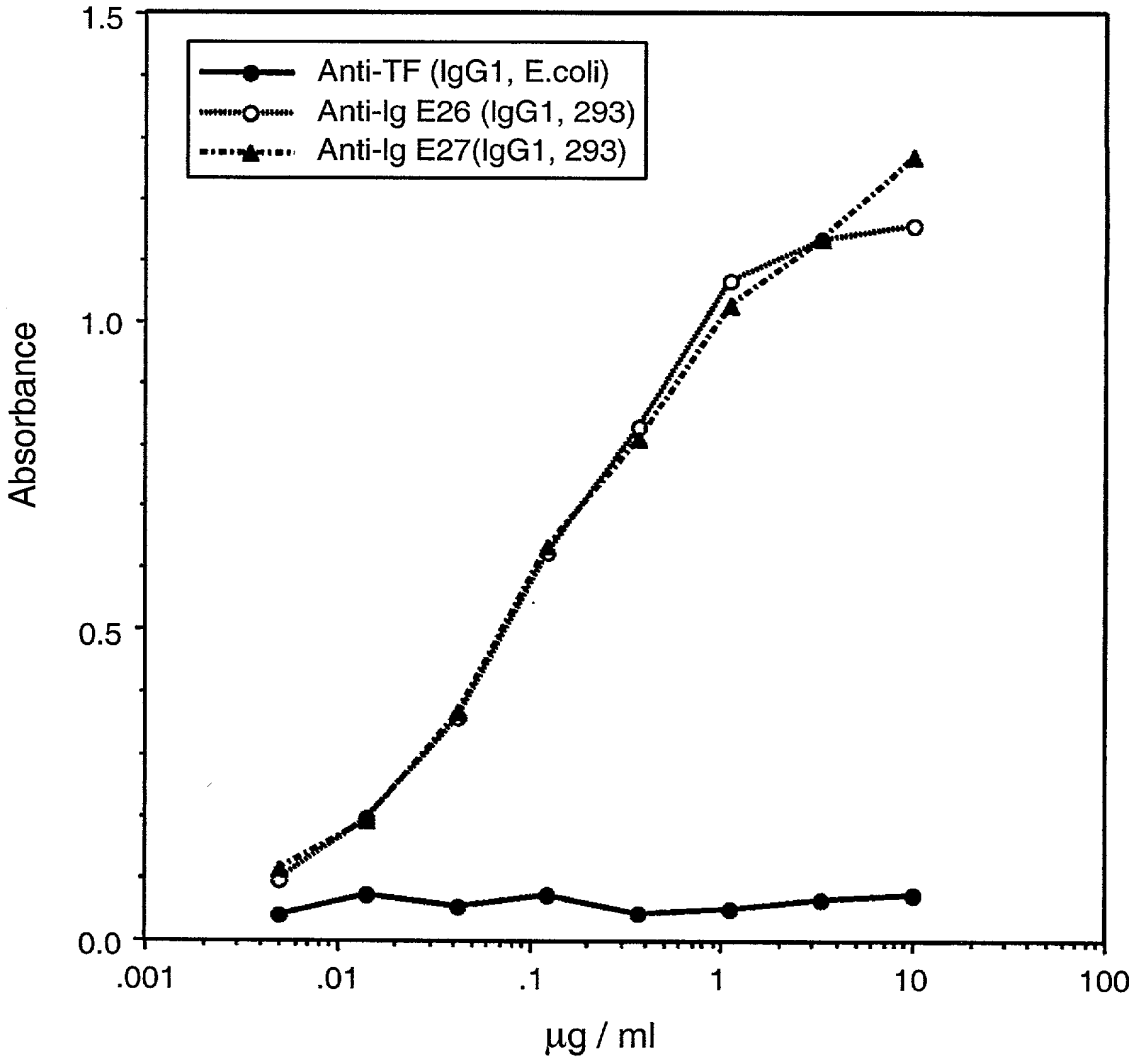

1.5
1.0
0.5
0.0
Absorbance
Anti-TF (IgG1, E.coli)
Anti-Ig E26 (IgG1, 293)
Anti-Ig E27(IgG1, 293)
.001
.01
.1
1
10
100
µg / ml

FIG._17

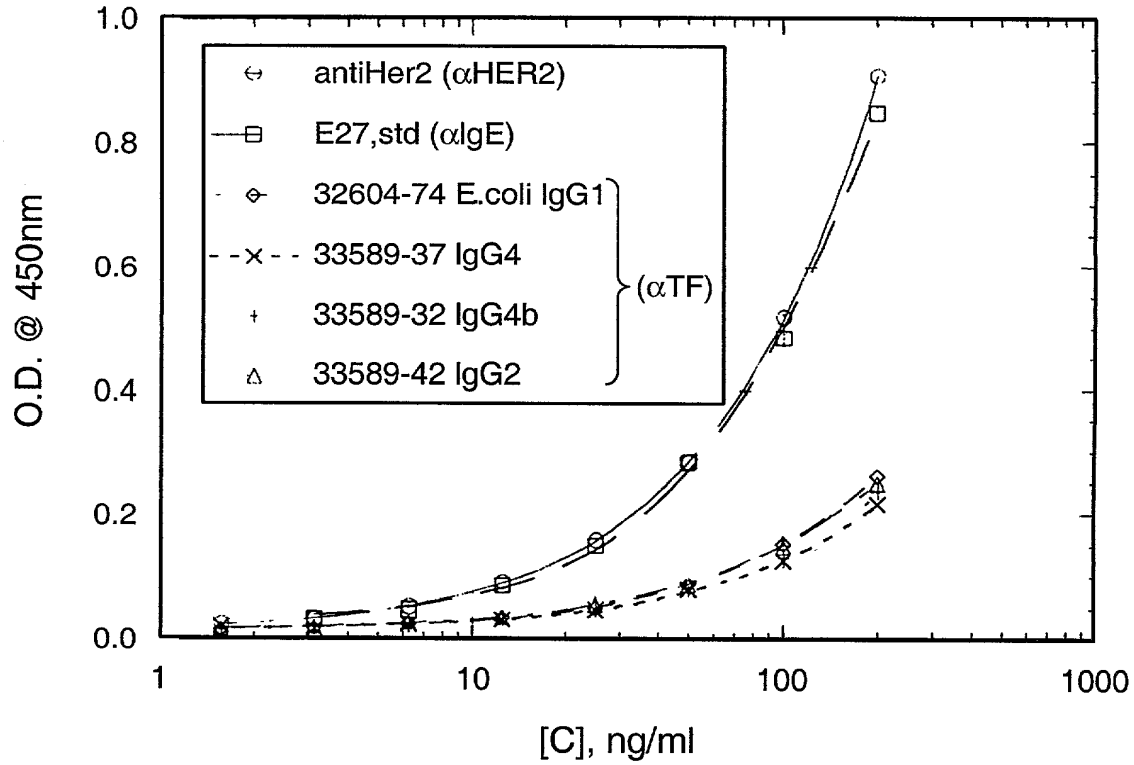

1.0
0.8
0.6
0.4
0.2
0.0
O.D. @ 450nm
1
10
100
1000
[C], ng/ml
antiHer2 (αHER2)
E27,std (αIgE)
32604-74 E.coli IgG1
33589-37 IgG4
33589-32 IgG4b
33589-42 IgG2
(αTF)

FIG._18

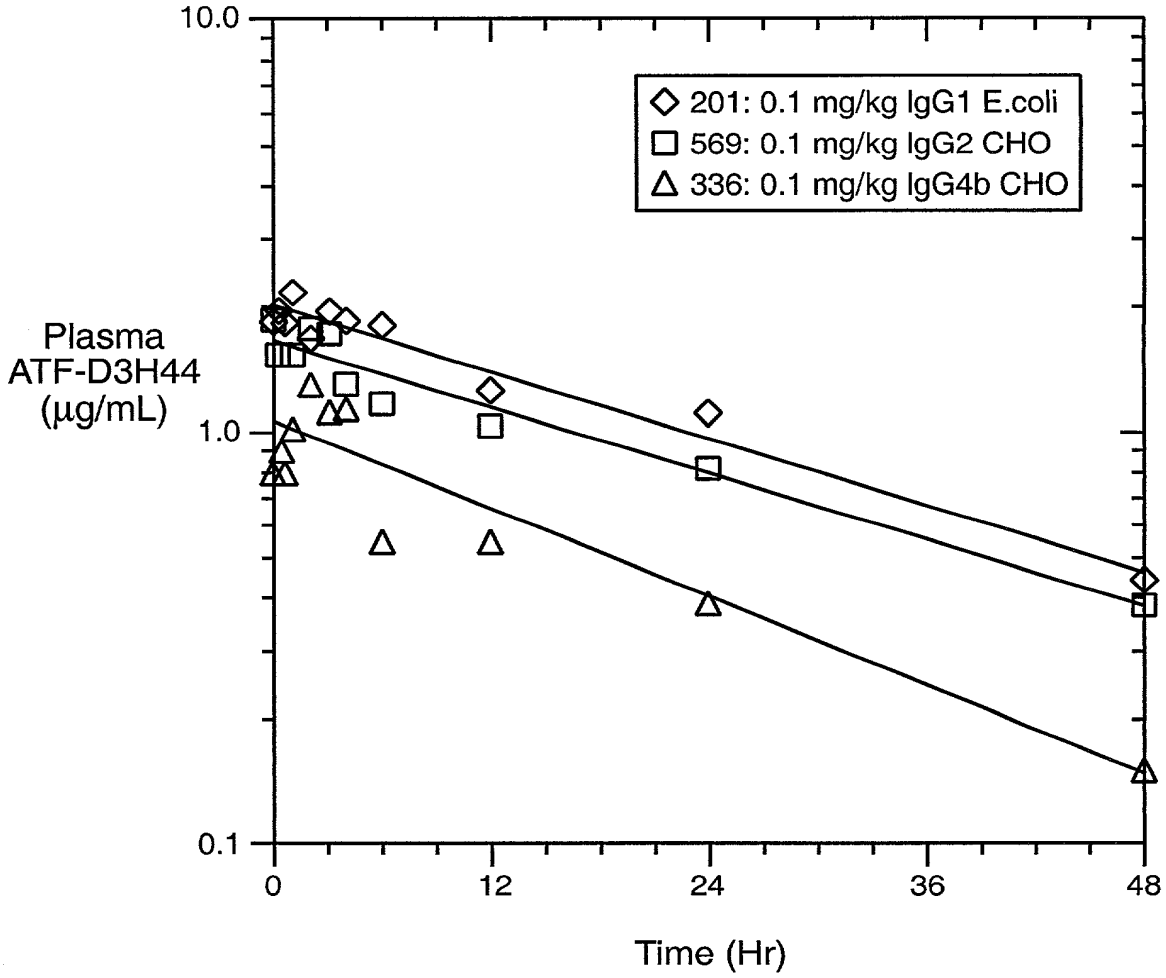

10.0
1.0
0.1
Plasma
ATF-D3H44
(µg/mL)
201: 0.1 mg/kg IgG1 E.coli
569: 0.1 mg/kg IgG2 CHO
336: 0.1 mg/kg IgG4b CHO
0
12
24
36
48
Time (Hr)

FIG._19

```
   1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT
     CTTAAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTTAG AGTAACGACT CAACAATAAA TTCGAACGGG TTTTTCTTCT TCTCAGCTTA

 101 GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG
     CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GACGTTACGA AGCGTTATAC CGCGTTTTAC TGGTTGTCGC CAACTAACTA GTCCATCTCC

 201 GGGCGCTGTA CGAGGTAAAG CCCGATGCCA GCATTCCTGA CGACGATACG GAGCTGCTGC GCGATTACGT AAAGAAGTTA TTGAAGCATC CTCGTCAGTA
     CCCGCGACAT GCTCCATTTC GGGCTACGGT CGTAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT

 301 AAAAGTTAAT CTTTTCAACA GCTGTCATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT TGTTTTTATT TTTTAATGTA TTTGTAACTA GTACGCAAGT
     TTTTCAATTA GAAAAGTTGT CGACAGTATT TCAACAGTGC CGGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT AAACATTGAT CATGCGTTCA

 401 TCACGTAAAA AGGGTATCTA GAATTATGAA GAAGAATATC GCATTTCTTC TTGCATCTAT GTTCGTTTTT TCTATTGCTA CAAACGCGTA CGCTGATATC
     AGTGCATTTT TCCCATAGAT CTTAATACTT CTTCTTATAG CGTAAAGAAG AACGTAGATA CAAGCAAAAA AGATAACGAT GTTTGCGCAT GCGACTATAG
   1                                 M  K  K  N  I  A  F  L  L  A  S  M  F  V  F  S  I  A  T  N  A  Y  A  D  I
                                     ^STII Signal Sequence TIR~1                                  Anti-Tissue Factor Light Chain^

 501 CAGATGACCC AGTCCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCAGAGCCA GTCGCGACAT CAAGAGCTAT CTGAACTGGT
     GTCTACTGGG TCAGGGGCTC GAGGGACAGG CGGAGACACC CGCTATCCCA GTGGTAGTGG ACGTCTCGGT CAGCGCTGTA GTTCTCGATA GACTTGACCA
  26 Q  M  T  Q   S  P  S   S  L  S   A  S  V  G   D  R  V   T  I  T   C  R  A  S   R  D  I   K  S  Y   L  N  W  Y

 601 ATCAACAGAA ACCAGGAAAA GCTCCGAAAG TACTGATTTA CTATGCTACT AGTCTCGCTG AAGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC
     TAGTTGTCTT TGGTCCTTTT CGAGGCTTTC ATGACTAAAT GATACGATGA TCAGAGCGAC TTCCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG
  60   Q  Q  K   P  G  K   A  P  K  V   L  I  Y   Y  A  T   S  L  A  E   G  V  P   S  R  F   S  G  S  G   S  G  T

 701 GGATTACACT CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTCT TCAGCACGGA GAGTCTCCAT GGACATTTGG ACAGGGTACC
     CCTAATGTGA GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAGA AGTCGTGCCT CTCAGAGGTA CCTGTAAACC TGTCCCATGG
  93  D  Y  T   L  T  I  S   S  L  Q   P  E  D   F  A  T  Y   Y  C  L   Q  H  G   E  S  P  W   T  F  G   Q  G  T

 801 AAGGTGGAGA TCAAACGAAC TGTGGCTGCA CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT GTGTGCCTGC
     TTCCACCTCT AGTTTGCTTG ACACCGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA CACACGGACG
 126 K  V  E  I   K  R  T   V  A  A   P  S  V  F   I  F  P   P  S  D   E  Q  L  K   S  G  T   A  S  V   V  C  L  L

 901 TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA
     ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT
 160   N  N  F   Y  P  R   E  A  K  V   Q  W  K   V  D  N   A  L  Q  S   G  N  S   Q  E  S   V  T  E  Q   D  S  K

1001 GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
     CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
 193  D  S  T   Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y   A  C  E  V   T  H  Q   G  L  S

1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG AGCTCGGTAC CCGGGGATCT AGGCCTAACG
     AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGATTGC
 226 S  P  V  T   K  S  F   N  R  G   E  C  O
```

FIG._20a

```
1201 CTCGGTTGCC GCCGGGCGTT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
     GAGCCAACGG CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA

1301 CGCAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGGG GGCGCTGTAC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
     GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCGCGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC

1401 AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA
     TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT

1501 TAGTCGCTTT GTTTTTATTT TTTAATGTAT TTGTAACTAG TACGCAAGTT CACGTAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
     ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCGTTCAA GTGCATTTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAAGAAGA
   1                                                                                  M  K  K  N  I  A  F  L  L
                                                                                     ^STII Signal Sequence TIR~1

1601 TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGCGTAC GCTGAGGTTC AGCTGGTGGA GTCTGGCGGT GGCCTGGTGC AGCCAGGGGG CTCACTCCGT
     ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGCGCATG CGACTCCAAG TCGACCACCT CAGACCGCCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA
  10 A  S  M  F  V  F  S  I  A  T  N  A  Y  A  E  V  Q  L  V  E  S  G  G  G  L  V  Q  P  G  G  S  L  R
                                                                     ^Anti-Tissue Factor Heavy Chain

1701 TTGTCCTGTG CAGCTTCTGG CTTCAATATT AAGGAGTACT ACATGCACTG GGTCCGTCAG GCCCCGGGTA AGGGCCTGGA ATGGGTTGGA TTGATTGATC
     AACAGGACAC GTCGAAGACC GAAGTTATAA TTCCTCATGA TGTACGTGAC CCAGGCAGTC CGGGGCCCAT TCCCGGACCT TACCCAACCT AACTAACTAG
  43 L  S  C  A  A  S  G  F  N  I  K  E  Y  Y  M  H  W  V  R  Q  A  P  G  K  G  L  E  W  V  G  L  I  D  P

1801 CAGAGCAAGG CAACACGATC TATGACCCGA AGTTCCAGGA CCGTGCCACT ATAAGCGCTG ACAATTCCAA AAACACAGCA TACCTGCAGA TGAACAGCCT
     GTCTCGTTCC GTTGTGCTAG ATACTGGGCT TCAAGGTCCT GGCACGGTGA TATTCGCGAC TGTTAAGGTT TTTGTGTCGT ATGGACGTCT ACTTGTCGGA
  77   E  Q  G  N  T  I  Y  D  P  K  F  Q  D  R  A  T  I  S  A  D  N  S  K  N  T  A  Y  L  Q  M  N  S  L

1901 GCGTGCTGAG GACACTGCCG TCTATTATTG TGCTCGAGAC ACGGCCGCTT ACTTCGACTA CTGGGGTCAA GGAACCCTGG TCACCGTCTC CTCGGCCTCC
     CGCACGACTC CTGTGACGGC AGATAATAAC ACGAGCTCTG TGCCGGCGAA TGAAGCTGAT GACCCCAGTT CCTTGGGACC AGTGGCAGAG GAGCCGGAGG
 110 R  A  E  D  T  A  V  Y  Y  C  A  R  D  T  A  A  Y  F  D  Y  W  G  Q  G  T  L  V  T  V  S  S  A  S

2001 ACCAAGGGCC CATCGGTCTT CCCCCTGGCA CCCTCCTCCA AGAGCACCTC TGGGGGCACA GCGGCCCTGG GCTGCCTGGT CAAGGACTAC TTCCCCGAAC
     TGGTTCCCGG GTAGCCAGAA GGGGGACCGT GGGAGGAGGT TCTCGTGGAG ACCCCCGTGT CGCCGGGACC CGACGGACCA GTTCCTGATG AAGGGGCTTG
 143 T  K  G  P  S  V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L  G  C  L  V  K  D  Y  F  P  E  P

2101 CGGTGACGGT GTCGTGGAAC TCAGGCGCCC TGACCAGCGG CGTGCACACC TTCCCGGCTG TCCTACAGTC CTCAGGACTC TACTCCCTCA GCAGCGTGGT
     GCCACTGCCA CAGCACCTTG AGTCCGCGGG ACTGGTCGCC GCACGTGTGG AAGGGCCGAC AGGATGTCAG GAGTCCTGAG ATGAGGGAGT CGTCGCACCA
 177   V  T  V  S  W  N  S  G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G  L  Y  S  L  S  S  V  V

2201 GACTGTGCCC TCTAGCAGCT TGGGCACCCA GACCTACATC TGCAACGTGA ATCACAAGCC CAGCAACACC AAGGTGGACA AGAAAGTTGA GCCCAAATCT
     CTGACACGGG AGATCGTCGA ACCCGTGGGT CTGGATGTAG ACGTTGCACT TAGTGTTCGG GTCGTTGTGG TTCCACCTGT TCTTTCAACT CGGGTTTAGA
 210 T  V  P  S  S  S  L  G  T  Q  T  Y  I  C  N  V  N  H  K  P  S  N  T  K  V  D  K  K  V  E  P  K  S
```

FIG._20b

```
2301 TGTGACAAAA CTCACACATG CCCACCGTGC CCAGCACCTG AACTCCTGGG GGGACCGTCA GTCTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA
     ACACTGTTTT GAGTGTGTAC GGGTGGCACG GGTCGTGGAC TTGAGGACCC CCCTGGCAGT CAGAAGGAGA AGGGGGGTTT TGGGTTCCTG TGGGAGTACT
 243 C  D  K  T   H  T  C   P  P  C   P  A  P  E   L  L  G   G  P  S   V  F  L  F   P  P  K   P  K  D   T  L  M  I

2401 TCTCCCGGAC CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA GACCCTGAGG TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA
     AGAGGGCCTG GGGACTCCAG TGTACGCACC ACCACCTGCA CTCGGTGCTT CTGGGACTCC AGTTCAAGTT GACCATGCAC CTGCCGCACC TCCACGTATT
 277   S  R  T   P  E  V   T  C  V  V   V  D  V   S  H  E   D  P  E  V   K  F  N   W  Y  V   D  G  V  E   V  H  N

2501 TGCCAAGACA AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG TCAGCGTCCT CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC
     ACGGTTCTGT TTCGGCGCCC TCCTCGTCAT GTTGTCGTGC ATGGCACACC AGTCGCAGGA GTGGCAGGAC GTGGTCCTGA CCGACTTACC GTTCCTCATG
 310  A  K  T   K  P  R  E   E  Q  Y   N  S  T   Y  R  V  V   S  V  L   T  V  L   H  Q  D  W   L  N  G   K  E  Y

2601 AAGTGCAAGG TCTCCAACAA AGCCCTCCCA GCCCCCATCG AGAAAACCAT CTCCAAAGCC AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC
     TTCACGTTCC AGAGGTTGTT TCGGGAGGGT CGGGGGTAGC TCTTTTGGTA GAGGTTTCGG TTTCCCGTCG GGGCTCTTGG TGTCCACATG TGGGACGGGG
 343 K  C  K  V   S  N  K   A  L  P   A  P  I  E   K  T  I   S  K  A   K  G  Q  P   R  E  P   Q  V  Y   T  L  P  P

2701 CATCCCGGGA AGAGATGACC AAGAACCAGG TCAGCCTGAC CTGCCTGGTC AAAGGCTTCT ATCCCAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA
     GTAGGGCCCT TCTCTACTGG TTCTTGGTCC AGTCGGACTG GACGGACCAG TTTCCGAAGA TAGGGTCGCT GTAGCGGCAC CTCACCCTCT CGTTACCCGT
 377   S  R  E   E  M  T   K  N  Q  V   S  L  T   C  L  V   K  G  F  Y   P  S  D   I  A  V   E  W  E  S   N  G  Q

2801 GCCGGAGAAC AACTACAAGA CCACGCCTCC CGTGCTGGAC TCCGACGGCT CCTTCTTCCT CTACAGCAAG CTCACCGTGG ACAAGAGCAG GTGGCAGCAG
     CGGCCTCTTG TTGATGTTCT GGTGCGGAGG GCACGACCTG AGGCTGCCGA GGAAGAAGGA GATGTCGTTC GAGTGGCACC TGTTCTCGTC CACCGTCGTC
 410  P  E  N   N  Y  K  T   T  P  P   V  L  D   S  D  G  S   F  F  L   Y  S  K   L  T  V  D   K  S  R   W  Q  Q

2901 GGGAACGTCT TCTCATGCTC CGTGATGCAT GAGGCTCTGC ACAACCACTA CACGCAGAAG AGCCTCTCCC TGTCTCCGGG TAAATAAGCA TGCGACGGCC
     CCCTTGCAGA AGAGTACGAG GCACTACGTA CTCCGAGACG TGTTGGTGAT GTGCGTCTTC TCGGAGAGGG ACAGAGGCCC ATTTATTCGT ACGCTGCCGG
 443  G  N  V   F   S  C   S   V  M   H   E  A  L   H   N  H  Y   T  Q  K   S  L  S  L   S  P  G   K  O

3001 CTAGAGTCCC TAACGCTCGG TTGCCGCCGG GCGTTTTTTA TTGTTAACTC ATGTTTGACA GCTTATCATC GATAAGCTTT AATGCGGTAG TTTATCACAG
     GATCTCAGGG ATTGCGAGCC AACGGCGGCC CGCAAAAAAT AACAATTGAG TACAAACTGT CGAATAGTAG CTATTCGAAA TTACGCCATC AAATAGTGTC

3101 TTAAATTGCT AACGCAGTCA GGCACCGTGT ATGAAATCTA ACAATGCGCT CATCGTCATC CTCGGCACCG TCACCCTGGA TGCTGTAGGC ATAGGCTTGG
     AATTTAACGA TTGCGTCAGT CCGTGGCACA TACTTTAGAT TGTTACGCGA GTAGCAGTAG GAGCCGTGGC AGTGGGACCT ACGACATCCG TATCCGAACC
                                  ^Start Tet Resistance Coding Sequence

3201 TTATGCCGGT ACTGCCGGGC CTCTTGCGGG ATATCGTCCA TTCCGACAGC ATCGCCAGTC ACTATGGCGT GCTGCTAGCG CTATATGCGT TGATGCAATT
     AATACGGCCA TGACGGCCCG GAGAACGCCC TATAGCAGGT AAGGCTGTCG TAGCGGTCAG TGATACCGCA CGACGATCGC GATATACGCA ACTACGTTAA

3301
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FIG._20c

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  1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT
    CTTAAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTTAG AGTAACGACT CAACAATAAA TTCGAACGGG TTTTTCTTCT TCTCAGCTTA
101 GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG
    CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GACGTTACGA AGCGTTATAC CGCGTTTTAC TGGTTGTCGC CAACTAACTA GTCCATCTCC
201 GGGCGCTGTA CGAGGTAAAG CCCGATGCCA GCATTCCTGA CGACGATACG GAGCTGCTGC GCGATTACGT AAAGAAGTTA TTGAAGCATC CTCGTCAGTA
    CCCGCGACAT GCTCCATTTC GGGCTACGGT CGTAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT
301 AAAAGTTAAT CTTTTCAACA GCTGTCATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT TGTTTTTATT TTTAATGTA TTTGTAACTA GTACGCAAGT
    TTTTCAATTA GAAAAGTTGT CGACAGTATT TCAACAGTGC CGGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT AAACATTGAT CATGCGTTCA
401 TCACGTAAAA AGGGTATCTA GAATTATGAA GAAGAATATC GCATTTCTTC TTGCATCTAT GTTCGTTTTT TCTATTGCTA CAAACGCGTA CGCTGATATC
    AGTGCATTTT TCCCATAGAT CTTAATACTT CTTCTTATAG CGTAAAGAAG AACGTAGATA CAAGCAAAAA AGATAACGAT GTTTGCGCAT GCGACTATAG
  1                          M  K  K  N  I  A  F  L  L  A  S  M  F  V  F  S  I  A  T  N  A  Y  A  D  I
                             ^STII Signal TIR ~1                                          Anti-VEGF Light chain^
501 CAGTTGACCC AGTCCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCAGCGCAA GTCAGGATAT TAGCAACTAT TTAAACTGGT
    GTCAACTGGG TCAGGGGCTC GAGGGACAGG CGGAGACACC CGCTATCCCA GTGGTAGTGG ACGTCGCGTT CAGTCCTATA ATCGTTGATA AATTTGACCA
 26 Q  L  T  Q   S  P  S   S  L  S   A  S  V  G   D  R  V   T  I  T   C  S  A  S   Q  D  I   S  N  Y   L  N  W  Y
601 ATCAACAGAA ACCAGGAAAA GCTCCGAAAG TACTGATTTA CTTCACCTCC TCTCTCCACT CTGGAGTCCC TTCTCGCTTC TCTGGATCCG GTTCTGGGAC
    TAGTTGTCTT TGGTCCTTTT CGAGGCTTTC ATGACTAAAT GAAGTGGAGG AGAGAGGTGA GACCTCAGGG AAGAGCGAAG AGACCTAGGC CAAGACCCTG
 60   Q  Q  K   P  G  K   A  P  K  V   L  I  Y   F  T  S   S  L  H  S   G  V  P   S  R  F   S  G  S  G   S  G  T
701 GGATTTCACT CTGACCATCA GCAGTCTGCA GCCAGAAGAC TTCGCAACTT ATTACTGTCA ACAGTATAGC ACCGTGCCGT GGACGTTTGG ACAGGGTACC
    CCTAAAGTGA GACTGGTAGT CGTCAGACGT CGGTCTTCTG AAGCGTTGAA TAATGACAGT TGTCATATCG TGGCACGGCA CCTGCAAACC TGTCCCATGG
 93  D  F  T   L  T  I  S   S  L  Q   P  E  D   F  A  T  Y   Y  C  Q   Q  Y  S   T  V  P  W   T  F  G   Q  G  T
801 AAGGTGGAGA TCAAACGAAC TGTGGCTGCA CCATCTGTCT TCATCTTCCC GCCATCTGAT GAGCAGTTGA AATCTGGAAC TGCTTCTGTT GTGTGCCTGC
    TTCCACCTCT AGTTTGCTTG ACACCGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG ACGAAGACAA CACACGGACG
126 K  V  E  I   K  R  T   V  A  A   P  S  V  F   I  F  P   P  S  D   E  Q  L  K   S  G  T   A  S  V   V  C  L  L
901 TGAATAACTT CTATCCCAGA GAGGCCAAAG TACAGTGGAA GGTGGATAAC GCCCTCCAAT CGGGTAACTC CCAGGAGAGT GTCACAGAGC AGGACAGCAA
    ACTTATTGAA GATAGGGTCT CTCCGGTTTC ATGTCACCTT CCACCTATTG CGGGAGGTTA GCCCATTGAG GGTCCTCTCA CAGTGTCTCG TCCTGTCGTT
160   N  N  F   Y  P  R   E  A  K  V   Q  W  K   V  D  N   A  L  Q  S   G  N  S   Q  E  S   V  T  E  Q   D  S  K
1001 GGACAGCACC TACAGCCTCA GCAGCACCCT GACGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG TCACCCATCA GGGCCTGAGC
    CCTGTCGTGG ATGTCGGAGT CGTCGTGGGA CTGCGACTCG TTTCGTCTGA TGCTCTTTGT GTTTCAGATG CGGACGCTTC AGTGGGTAGT CCCGGACTCG
193  D  S  T   Y  S  L  S   S  T  L   T  L  S   K  A  D  Y   E  K  H   K  V  Y   A  C  E  V   T  H  Q   G  L  S
1101 TCGCCCGTCA CAAAGAGCTT CAACAGGGGA GAGTGTTAAT TAAATCCTCT ACGCCGGACG CATCGTGGCG AGCTCGGTAC CCGGGGATCT AGGCCTAACG
    AGCGGGCAGT GTTTCTCGAA GTTGTCCCCT CTCACAATTA ATTTAGGAGA TGCGGCCTGC GTAGCACCGC TCGAGCCATG GGCCCCTAGA TCCGGATTGC
226 S  P  V  T   K  S  F   N  R  G   E  C  O
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FIG._21a

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1201 CTCGGTTGCC GCCGGGCGTT TTTTATTGTT GCCGACGCGC ATCTCGAATG AACTGTGTGC GCAGGTAGAA GCTTTGGAGA TTATCGTCAC TGCAATGCTT
     GAGCCAACGG CGGCCCGCAA AAAATAACAA CGGCTGCGCG TAGAGCTTAC TTGACACACG CGTCCATCTT CGAAACCTCT AATAGCAGTG ACGTTACGAA
1301 CGCAATATGG CGCAAAATGA CCAACAGCGG TTGATTGATC AGGTAGAGGG GGCGCTGTAC GAGGTAAAGC CCGATGCCAG CATTCCTGAC GACGATACGG
     GCGTTATACC GCGTTTTACT GGTTGTCGCC AACTAACTAG TCCATCTCCC CCGCGACATG CTCCATTTCG GGCTACGGTC GTAAGGACTG CTGCTATGCC
1401 AGCTGCTGCG CGATTACGTA AAGAAGTTAT TGAAGCATCC TCGTCAGTAA AAAGTTAATC TTTTCAACAG CTGTCATAAA GTTGTCACGG CCGAGACTTA
     TCGACGACGC GCTAATGCAT TTCTTCAATA ACTTCGTAGG AGCAGTCATT TTTCAATTAG AAAAGTTGTC GACAGTATTT CAACAGTGCC GGCTCTGAAT
1501 TAGTCGCTTT GTTTTTATTT TTTAATGTAT TTGTAACTAG TACGCAAGTT CACGTAAAAA GGGTATCTAG AATTATGAAG AAGAATATCG CATTTCTTCT
     ATCAGCGAAA CAAAAATAAA AAATTACATA AACATTGATC ATGCGTTCAA GTGCATTTTT CCCATAGATC TTAATACTTC TTCTTATAGC GTAAAGAAGA
   1                                                                                  M  K  K  N  I  A  F  L  L
                                                                                    ^STII Signal TIR~1
1601 TGCATCTATG TTCGTTTTTT CTATTGCTAC AAACGCGTAC GCTGAGGTTC AGCTGGTGGA GTCTGGCGGT GGCCTGGTGC AGCCAGGGGG CTCACTCCGT
     ACGTAGATAC AAGCAAAAAA GATAACGATG TTTGCGCATG CGACTCCAAG TCGACCACCT CAGACCGCCA CCGGACCACG TCGGTCCCCC GAGTGAGGCA
  10 A  S  M  F  V  F  S  I  A  T  N  A  Y  A  E  V  Q  L  V  E  S  G  G  G  L  V  Q  P  G  G  S  L  R
                                                ^Anti-VEGF Heavy Chain
1701 TTGTCCTGTG CAGCTTCTGG CTACGACTTC ACGCACTACG GTATGAACTG GGTCCGTCAG GCCCCGGGTA AGGGCCTGGA ATGGGTTGGA TGGATTAACA
     AACAGGACAC GTCGAAGACC GATGCTGAAG TGCGTGATGC CATACTTGAC CCAGGCAGTC CGGGGCCCAT TCCCGGACCT TACCCAACCT ACCTAATTGT
  43 L  S  C  A  A  S  G  Y  D  F  T  H  Y  G  M  N  W  V  R  Q  A  P  G  K  G  L  E  W  V  G  W  I  N  T
1801 CCTATACCGG TGAACCGACC TATGCTGCGG ATTTCAAACG TCGTTTCACT TTTTCTTTAG ACACCTCCAA AAGCACAGCA TACCTGCAGA TGAACAGCCT
     GGATATGGCC ACTTGGCTGG ATACGACGCC TAAAGTTTGC AGCAAAGTGA AAAAGAAATC TGTGGAGGTT TTCGTGTCGT ATGGACGTCT ACTTGTCGGA
  77  Y  T  G  E  P  T  Y  A  A  D  F  K  R  R  F  T  F  S  L  D  T  S  K  S  T  A  Y  L  Q  M  N  S  L
1901 GCGCGCTGAG GACACTGCCG TCTATTACTG TGCAAAGTAC CCGTACTATT ACGGCACGAG CCACTGGTAT TTCGACGTCT GGGGTCAAGG AACCCTGGTC
     CGCGCGACTC CTGTGACGGC AGATAATGAC ACGTTTCATG GGCATGATAA TGCCGTGCTC GGTGACCATA AAGCTGCAGA CCCCAGTTCC TTGGGACCAG
 110 R  A  E  D  T  A  V  Y  Y  C  A  K  Y  P  Y  Y  Y  G  T  S  H  W  Y  F  D  V  W  G  Q  G  T  L  V
2001 ACCGTCTCCT CGGCCTCCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC TGCCTGGTCA
     TGGCAGAGGA GCCGGAGGTG GTTCCCGGGT AGCCAGAAGG GGGACCGTGG GAGGAGGTTC TCGTGGAGAC CCCCGTGTCG CCGGGACCCG ACGGACCAGT
 143 T  V  S  S  A  S  T  K  G  P  S  V  F  P  L  A  P  S  S  K  S  T  S  G  G  T  A  A  L  G  C  L  V  K
2101 AGGACTACTT CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA
     TCCTGATGAA GGGGCTTGGC CACTGCCACA GCACCTTGAG TCCGCGGGAC TGGTCGCCGC ACGTGTGGAA GGGCCGACAG GATGTCAGGA GTCCTGAGAT
 177  D  Y  F  P  E  P  V  T  V  S  W  N  S  G  A  L  T  S  G  V  H  T  F  P  A  V  L  Q  S  S  G  L  Y
2201 CTCCCTCAGC AGCGTGGTGA CTGTGCCCTC TAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG
     GAGGGAGTCG TCGCACCACT GACACGGGAG ATCGTCGAAC CCGTGGGTCT GGATGTAGAC GTTGCACTTA GTGTTCGGGT CGTTGTGGTT CCACCTGTTC
 210 S  L  S  S  V  V  T  V  P  S  S  S  L  G  T  Q  T  Y  I  C  N  V  N  H  K  P  S  N  T  K  V  D  K
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FIG._21b

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2301 AAAGTTGAGC CCAAATCTTG TGACAAAACT CACACATGCC CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCCTCTTC CCCCCAAAAC
     TTTCAACTCG GGTTTAGAAC ACTGTTTTGA GTGTGTACGG GTGGCACGGG TCGTGGACTT GAGGACCCCC CTGGCAGTCA GAAGGAGAAG GGGGGTTTTG
 243 K  V  E  P     K  S  C     D  K  T     H  T  C  P     P  C  P     A  P  E     L  L  G  G     P  S  V     F  L  F     P  P  K  P
2401 CCAAGGACAC CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA CCCTGAGGTC AAGTTCAACT GGTACGTGGA
     GGTTCCTGTG GGAGTACTAG AGGGCCTGGG GACTCCAGTG TACGCACCAC CACCTGCACT CGGTGCTTCT GGGACTCCAG TTCAAGTTGA CCATGCACCT
 277    K  D  T     L  M  I     S  R  T  P     E  V  T     C  V  V     V  D  V  S     H  E  D     P  E  V     K  F  N  W     Y  V  D
2501 CGGCGTGGAG GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA ACAGCACGTA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA CCAGGACTGG
     GCCGCACCTC CACGTATTAC GGTTCTGTTT CGGCGCCCTC CTCGTCATGT TGTCGTGCAT GGCACACCAG TCGCAGGAGT GGCAGGACGT GGTCCTGACC
 310  G  V  E     V  H  N  A     K  T  K     P  R  E     E  Q  Y  N     S  T  Y     R  V  V     S  V  L  T     V  L  H     Q  D  W
2601 CTGAATGGCA AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC
     GACTTACCGT TCCTCATGTT CACGTTCCAG AGGTTGTTTC GGGAGGGTCG GGGGTAGCTC TTTTGGTAGA GGTTTCGGTT TCCCGTCGGG GCTCTTGGTG
 343 L  N  G  K     E  Y  K     C  K  V     S  N  K  A     L  P  A     P  I  E     K  T  I  S     K  A  K     G  Q  P     R  E  P  Q
2701 AGGTGTACAC CCTGCCCCCA TCCCGGGAAG AGATGACCAA GAACCAGGTC AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA
     TCCACATGTG GGACGGGGGT AGGGCCCTTC TCTACTGGTT CTTGGTCCAG TCGGACTGGA CGGACCAGTT TCCGAAGATA GGGTCGCTGT AGCGGCACCT
 377    V  Y  T     L  P  P     S  R  E  E     M  T  K     N  Q  V     S  L  T  C     L  V  K     G  F  Y     P  S  D  I     A  V  E
2801 GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT ACAGCAAGCT CACCGTGGAC
     CACCCTCTCG TTACCCGTCG GCCTCTTGTT GATGTTCTGG TGCGGAGGGC ACGACCTGAG GCTGCCGAGG AAGAAGGAGA TGTCGTTCGA GTGGCACCTG
 410  W  E  S     N  G  Q  P     E  N  N     Y  K  T     T  P  P  V     L  D  S     D  G  S     F  F  L  Y     S  K  L     T  V  D
2901 AAGAGCAGGT GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA
     TTCTCGTCCA CCGTCGTCCC CTTGCAGAAG AGTACGAGGC ACTACGTACT CCGAGACGTG TTGGTGATGT GCGTCTTCTC GGAGAGGGAC AGAGGCCCAT
 443 K  S  R  W     Q  Q  G     N  V  F     S  C  S  V     M  H  E     A  L  H     N  H  Y  T     Q  K  S     L  S  L     S  P  G  K
3001 AATAAGCATG CGACGGCCCT AGAGTCCCTA ACGCTCGGTT GCCGCCGGGC GTTTTTTATT GTTAACTCAT GTTTGACAGC TTATCATCGA TAAGCTTTAA
     TTATTCGTAC GCTGCCGGGA TCTCAGGGAT TGCGAGCCAA CGGCGGCCCG CAAAAAATAA CAATTGAGTA CAAACTGTCG AATAGTAGCT ATTCGAAATT
 477   O
3101 TGCGGTAGTT TATCACAGTT AAATTGCTAA CGCAGTCAGG CACCGTGTAT GAAATCTAAC AATGCGCTCA TCGTCATCCT CGGCACCGTC ACCCTGGATG
     ACGCCATCAA ATAGTGTCAA TTTAACGATT GCGTCAGTCC GTGGCACATA CTTTAGATTG TTACGCGAGT AGCAGTAGGA GCCGTGGCAG TGGGACCTAC
                                                                ^Start Tet Resistance Coding Sequence
3201 CTGTAGGCAT AGGCTTGGTT ATGCCGGTAC TGCCGGGCCT CTTGCGGGAT ATCGTCCATT CCGACAGCAT CGCCAGTCAC TATGGCGTGC TGCTAGCGCT
     GACATCCGTA TCCGAACCAA TACGGCCATG ACGGCCCGGA GAACGCCCTA TAGCAGGTAA GGCTGTCGTA GCGGTCAGTG ATACCGCACG ACGATCGCGA
3301
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FIG._21c

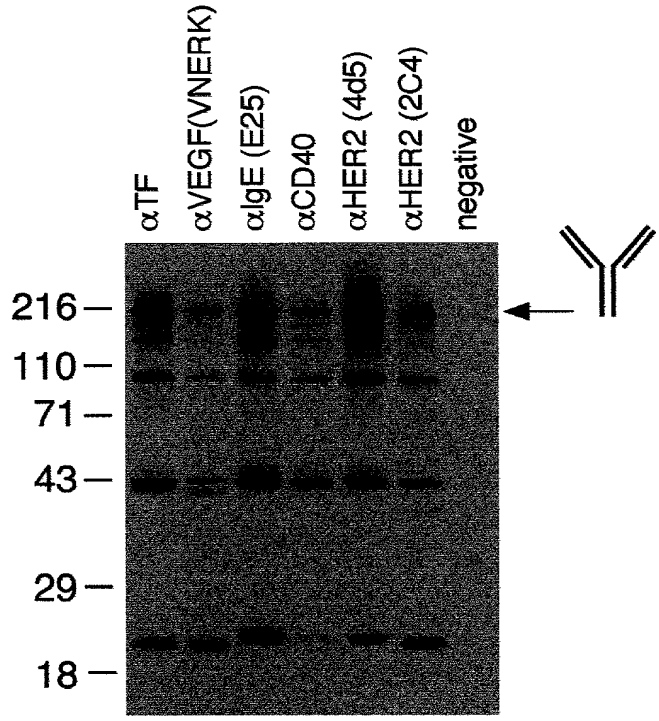

FIG._22A

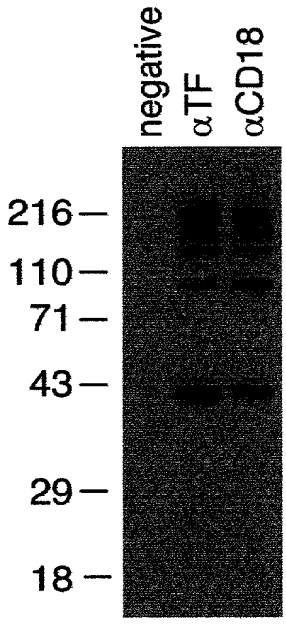

FIG._22B